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EXAMINER	
KELLY, ROBERT M	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/033,491	ZHANG ET AL.	
	Examiner	Art Unit	
	Robert M Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 August 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *70-226* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *70-226* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 August 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/17/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 70-226 are pending.

Election/Restrictions

Applicant's election without traverse of the species (a) CMV IE; and (b) p53, in the reply filed on 23 July 2004 is acknowledged.

Claims 70-226 will be considered for the aforementioned species.

Information Disclosure Statement

Although all the cited documents of Applicant's information disclosure statements have been considered, a line has been drawn through the citation to the PCT search report. This is because the PCT search report is not a publication. All cited documents that are considered are published on any patent that would issue from the application, and must be available for the reader to access. Because the PCT search report is not a publication, it is not publicly available, and so the line was drawn through the citation to avoid any possible publishing of such report citation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground

provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70-226 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12 and 31 of U.S. Patent No. 6,726,907. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims 70-226 of the instant Application encompass methods of treating patients with adenoviral vectors, comprising the obtaining of a vector and the administration of the vector the patient. The vectors may be obtained by many methods.

Claims 12 and 31 of the Patent encompass pharmaceutically acceptable formulations of similar vectors. Such vectors must have less than 400 pg of contaminating nucleic acid per 10^{10} PFU virus and greater than about 60 pg of contaminating nucleic acid per 10^{10} PFU virus. Furthermore, BSA concentrations may be undetectable by standard western blot assays. Moreover, it is noted that:

(i) the other claims also encompass similar limitations on the adenoviruses to those found in the present application with respect to the transgenes, promoters;

(ii) the BSA concentrations are specifically embraced by dependent claims of the instant application (e.g., Claims 78, 109, 140, 171, and 202); and

(iii) the low levels of contaminating nucleic acid are embraced by some of the dependent claims of the instant application (e.g., Claims 73-74, 104-105, 135-136, 166-167, and 197-198).

Because the adenoviruses formulated in pharmaceutically-acceptable solutions are disclosed in each of the specifications as having only one use, i.e., treating patients; because the formulated adenoviruses in pharmaceutically acceptable solutions are made by the same methods; because the specifications teach the same transgenes and promoters and diseases; and because the instantly claimed methods of treatment are not distinguished in any material way from distinguish that of the only disclosed use for pharmaceutically acceptable formulations of adenovirus; and such methods of use are coextensive in both the instant application and the patent, Claims 12 and 35 of the patent are obvious over the methods of treatment in the instant application.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 70-226 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 13-28, 31, and 33-37 of copending Application No. 09/203,078. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Claims 70-226 of the instant Application encompass methods of treating patients with adenoviral vectors, comprising the obtaining of a vector and the administration of the vector the patient. The vectors may be obtained by many methods.

Claims 13-28 of copending Application No. 09/203,078 comprise purified adenovirus in pharmaceutically acceptable solutions, which adenovirus has been obtained by methods that embrace many of the same methods of obtaining adenoviruses in the instant application. Such purification may be by chromatographic methods, which are taught in both specifications, may contain the same transgenes and promoters taught in the instant application's claims, and may have the same host cells for growth and may have the same types of replication deficient adenovirus as in the instant Application's claims. Claims 31 and 33-37 embrace adenoviruses in pharmaceutically acceptable solutions which, when obtained have many of the same characteristics, and are not exclusive of, the characteristics claimed in the instant application. Moreover, Claim 33 specifically embraces treating a patient with the solution, and claims 34-37 similar characteristics of treatment claimed in the instant application.

Therefore, because the pharmaceutically acceptable solutions and methods of treatment in copending Application No. 09/203,078 encompass the same methods of treatment as in the instant Application, these claims encompass common subject matter.

Hence, it would have been obvious for one of skill in the art to make the methods of Applicant's claims from the claimed pharmaceutically acceptable solutions of copending Application No. 09/203,078. One of skill in the art would have been motivated to do so because Applicant's instantly-claimed embodiments are embraced by copending Application No.

09/203,078. Moreover, one of skill in the art would have had a reasonable expectation of success, because both applications teach these embodiments.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 70-226 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 70, 101, 132, 163, and 194 comprise methods of treating patients with adenoviral vectors; however, there is no positive step of treatment. As such it is also not clear how those steps performed in the method provide for any treatment.

Claims 71-100, 102-131, 133-162, 164-193, and 195-226 are rejected for depending from Claims 70, 101, 132, 163, and 194, respectively, while similarly not providing any positive step of treatment.

Claims 71, 102, 133, 164, and 195 each recites the limitation "the starting PFU" in Claims 70, 101, 132, 163, and 194, respectively. There is insufficient antecedent basis for this limitation in the claims.

Claims 78, 109, 140, 171, and 202 each recite the limitation "below the detection level of a western blot assay." The metes and bounds of this limitation are not clear.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 70-226 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The invention of Claims 70-226 encompasses:

(i) a therapeutic adenovirus (Claims 70-226);

(ii) any promoter (Claims 86, 117, 148, 179, and 210); and

(iii) any therapeutic gene (Claims 88, 119, 150, 181, and 212).

The embodiments of these claims are broad in scope, being defined on the basis of their effect, and not on any specific structure. The specification broadly discloses, adenoviral vectors that encode therapeutic proteins (e.g., p. 2, lines 14-16), six different promoters (e.g., p. 4, lines 24-26 and TABLE II), and thirteen antisense genes (e.g., p. 5, lines 5-8), and a number of different therapeutic genes (e.g., pp. 43-48) and antigens for vaccines (e.g., p. 50, lines 5-19).

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, no adenoviruses have been disclosed that are therapeutic

in and of themselves, and the six promoters, various antisense and therpeutic genes, do not provide any common structure from which to distinguish the various members of the genera. The specification does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics are that the gene provides a therapeutic effect (e.g., pp. 43-450) and the promoter effects transcription of the gene to which it is operatively linked (e.g., p. 50, last paragraph).

Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any therapeutic adenovirus, any

therapeutic gene, and any promoter, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 70-226 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of treating a cancer in a patient comprising a direct administration of an adenoviral vector, which vector comprises a promoter operably linked to a nucleotide sequence encoding wild-type p53, which administration causes the transformation of cancer cells and expression of such p53 transgene, thereby inhibiting the uncontrolled growth of the cancer, does not reasonably provide enablement for treating any disease by administering an adenoviral vector comprising any transgene, or any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Background

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple

factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention, and that, therefore, Applicant's claims are not enabled.

The Breadth of the Claims

Claims 70-226 are broad in scope. The following paragraphs will outline the breadth of these claims.

Independent Claims 70, 101, 132, 163, and 194 encompass a method of treating a patient with any therpeutic adenovirus composition, comprising obtaining a therapeutic adenovirus compoisition that has been prepared by a process that comprises growing host cells in media, providing nutrients to the host cells, infecting the host cells with any adenovirus, lysing the host cells, purifying the adenovirus from the lysate, formulating a therapeutic adenovirus composition, and administering the composition by any method to any patient. Claim 101

requires the growing of host cells to be in a bioreactor or on a microcarrier. Claim 132 requires the nutrients to be provided by perfusion or fed-batch or roller-bottle processes. Claim 163 requires the purification to be by any process than freeze-thaw. Claim 194 requires the purification to include a chromatography step, without the use of CsCl.

Dependent Claims 71-100, 102-131, 133-162, 164-193, and 195-226, which depend from 70, 101, 132, 163, and 194, respectively, include further alterations to the steps of obtaining an adenovirus composition, the incorporation of transgenes, promoters, and specific transgenes and promoters (it is noted that the present invention is considered only with respect to CMV-MIE promoter and the p53 transgene). However, for purposes of this rejection, these alterations of the steps of obtaining an adenoviral composition are immaterial, as the specification does not provide any reason to believe these compositions are materially distinct from those adenoviral compositions obtained from other methods.

Hence, because these claims encompass the treatment of any patient with any adenoviral vector or adenoviral vectors comprising p53-encoding sequences, and CMV-MIE promoters, which are administered by any method to treat the patient, the specification must flesh-out a wide area of knowledge, to a reasonable extent, so that one of skill in the art at the time of invention by Applicant (hereinafter the "Artisan") would able to practice the invention, and do so to its fully claimed scope, without an undue burden being imposed on such Artisan. Undue burden is typically found when the Artisan would have to perform large amounts of experimentation to find the working embodiments of Applicant's claimed invention, essentially amounting to the Artisan "inventing" the claimed invention himself or herself. As will be shown below the breadth of Applicant's claims (or that portion of the claims considered, specifically), is large

enough to provide for a series of unpredictabilities that the Artisan would have to overcome with respect to the vast majority of embodiments to which the claims are considered.

The Nature of the Invention

The nature of the invention is gene therapy, i.e., the use of vectors to genetically transform cells, and thereby treat a patient. The very nature of gene therapy is not generally enabling of new inventions in the field. The general nature of the invention has been this way for many years. The following paragraphs provide an eloquent analysis of the general nature of gene therapy. Although some of these articles date back over the past eight years, they are utilized because they provide a succinct and eloquent analysis of gene therapy, and the difficulties and unpredictabilities have still not been overcome by the art, as will be shown in the state of the prior art (next section), even though many more articles are published each month.

With regard to gene therapy, while progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be a difficulty as supported by numerous teachings available in the art. For example, Deonarain (1998) Expert Opin. Ther. Pat., 8: 53-69, indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequeate levels for a long enough period of time" (p. 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise but states that such techniques are even less efficient than viral gene delivery (p. 65, CONCLUSION). Verma (1997) Nature, 389: 239-242, reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (entire article). Verma also teaches

appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements target (p. 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery and this is the aspect we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression ... The use of viruses (viral vectors) is a powerful technique, because many of them have evolved a specific machinery to deliver DNA to cells. However, humans have an immune system to fight off the virus, and our attempts to deliver genes in viral vectors have been confronted by these host responses (e.g., p. 239, col. 3).

Further, Eck et al. (1996) Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, NY., pp. 77-101, states that the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced, are all important factors for a successful gene therapy (e.g., bridging pp. 81-82). In addition, Gorecki (2001) Expert Opin. Emerging Drugs 6(2): 187-98) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and stability of expression and immune responses to vectors and/or gene products" (e.g., ABSTRACT).

Lastly, with regard to adenoviruses without specific transgenes and promoters, no art of record demonstrates how such adenoviruses could effect treatment of any disease.

In reviewing the above-discussed problems, it is clear that the Artisan would therefore require, to make and/or use a new invention in the field, a showing to reasonable predict that enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment. Alternatively, direct examples of specific vectors, whether transformed *in vivo* or *ex vivo*, would overcome this showing for that specific method of administration to that specific species, because, if treatment is successful, it must have met these aforementioned requirements.

The State of the Prior Art

The prior art is similarly not generally enabling for new inventions in the field of gene therapy and the treatment of cancers with adenoviral vectors. The reasons are the same as that of the nature of the invention, as well as other unpredictabilities peculiar to this specific art.

Green, et al. (2002) Cancer Gene Therapy, 9 : 1036-42 provides a general overview of the treatment of cancers with adenoviral vectors.

The first issue which Green presents is one of targeting and of administration route: "The development of a targeted adenoviral vector, which can be delivered systemically, is one of the major challenges facing cancer gene therapy." (ABSTRACT). Moreover, clearance issues abound in the art too, "The virus is readily cleared from the bloodstream, can be neutralized by pre-existing antibodies, and has permissive cellular tropism." Lastly, although Applicant's

specification does not describe adenoviral vectors without transgenes that can treat cancer, Green describes conditionally-replicating adenoviruses, e.g., ONYX, which have, "shown limited efficacy, but there are several hurdles to overcome to achieve an effective tumor-specific system therapy." (Id.). In this abstract, Green has systemically demonstrated that there exist many unpredictabilities in the field, which echo that of the general nature of gene therapy: targeting, clearance, and tissue specificity.

With regard to actual treatments, mice being treated have similarly shown problems with delivery, due to clearance through the liver and preexisting immunity, which can cause the death of mice before any treatment could be effected (p. 1037, col. 1, paragraphs 2-3).

With regard to conditionally replicating vectors, a few approaches have been used, but these approaches are similarly not generally enabling of new inventions in the field. Specifically, the inhibition of p53 may be used to effect selective replication of adenoviral vectors (it is noted that this is in direct contrast the elected p53 gene, so those embodiments considered with regard to p53 would not be efficacious in this method). Moreover, several reports demonstrate that tumor-selective adenoviral vectors can replicate in wild-type p53-containing cells (p. 1038, col. 2, last paragraph). Other approaches use tissue-specific promoters to effect replication in particular tissue types (p. 1039, paragraph bridging columns). However, Applicant's specification has not even contemplated this approach, as they only discuss placing the essential genes of adenoviral replication under the control of a packing cell line, and not for the control of a specific tissue (e.g., p. 40, last paragraph).

Moreover, neither Green's publication, nor Applicant's specification, nor in any art of record, are any mutant forms of p53 described which would be efficacious in any form of

treatment. Hence, the Artisan would not be able to reasonably predict that any form of p53 could be used. (Such is discussed in further detail in the analysis of Applicant's provided guidance and direction.)

Green finishes the discussion with a listing of some key hurdles to overcome for effective gene therapy with adenoviral vectors and cancer, including problems with liver uptake, neutralizing antibodies, and the use of genes other than p53 for treating cancer (p. 1040, whole page).

From Green it is clear that the Artisan would not be able to reasonably predict that any method of administration would be efficacious for treating cancer with any adenoviral vector, particularly p53-encoding adenoviruses, because of problems with targeting, clearance and efficacy.

On the other hand, U.S. Patent 6,740,320 to Zhang, et al., filed 2 June 1995, patented 25 May 2004, describes the use of p53-encoding adenoviruses for treating cancer in animals comprising the direct administration of such vectors to the cancer (ABSTRACT). Zhang teaches the direct administration of such vectors (e.g., col. 16, lines 39-48).

Moreover, no art of record teaches the treatment of anything other than cancer with p53 expressing cells or selectively replicating cells.

Hence, although the art, in view of the nature of the invention, is generally enabling for treating cancers via direct administration of adenoviral vectors encoding p53 under the control of strong-constitutive promoter (e.g., CMV-MIE, col. 16, lines 5-12), the art is not enabling for treating any patient, by the administration, by any route, of any adenoviral vector. The reasons that the art, in view of the nature of gene therapy, raises a number of unpredictabilities such that

the artisan would not be able to predict that any particular claimed embodiment would be efficacious. These unpredictabilities include: whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment and whether immune responses would kill the patient before therapy could be effected.

Therefore, the level of disclosure by Applicant, by way of specific guidance and direction, and/or example, would be required to provide enough information for the artisan to overcome the unpredictabilities discussed above. However, as will be shown, such disclosure has not been provided.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed to its fully-claimed scope without undue experimentation.

The Level of Predictability in the Art

Because the art, as shown above, does not disclose enough to reasonably predict whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and

that such expression occurs for a long enough period of time to effect treatment and whether immune responses would kill the patient before therapy could be effected, the Artisan could not predict, in the absence of proof to the contrary, that such applications would be efficacious in any particular therapeutic application.

Hence, absent a strong showing of guidance and direction and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled for its fully claimed scope.

The Amount of Direction and Guidance Provided by Applicant

The specification broadly discusses methods of the production and purification of adenoviruses (pp. 2-8), broad discussion of uses of adenoviral vectors and their preparation (pp. 11-12), host cells for the growing of adenoviruses (pp. 12-14), growth of such cells and vectors in selection media (pp. 14-16), cell culture systems (pp. 17-28), methods of harvesting cell lysates (pp. 29-36), concentration and filtration of adenoviruses from lysates (pp. 37-38), viral infection for obtaining suitable viruses (pp. 38-43), engineering viral vectors with genes (pp. 43-48),antisense constructs (pp. 48-50), and antigens for vaccines (p. 50). Further broad discussion is given for promoters, enhancers, and polyA tails (pp. 50-57), methods of gene transfer (pp. 57-60), the removal of nucleic acid contaminants (pp. 60-61), and viral purification (pp. 61-72), pharmaceutical compositions (pp. 72-75).

Moreover, from the specification and the state of the prior art, the Artisan would not able to reasonably predict that any p53 gene would produce efficacious protein for Applicant's invention. As noted in the analysis of the prior art, Green, nor any Art of record, describes any working mutant forms of p53 (discussed with regard to Green, in the state of the prior art).

Furthermore, Applicant discusses p53 on pages 43-45 of the Specification, stating that "Wild-type p53 is recognized as an important growth regulator in many types of cells" (p. 44, line 16). Also, Applicant cites a number of mutations that produce non-functioning p53, i.e., contributes to uncontrolled cell growth, and only provides wild-type p53 in the context of arresting uncontrolled cellular growth (pp. 43-45). Hence, because the majority of mutant p53 forms produce uncontrolled cellular growth, the Artisan would not be able to reasonably predict that any form of p53 would be able to inhibit cellular growth, except wild type p53.

However, such broad discussion does not provide the specific direction and guidance the Artisan would require to reasonably predict whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment and whether immune responses would kill the patient before therapy could be effected, and whether any particular form of p53 except wild-type would be efficacious, for any particular embodiment. Therefore, absent a strong showing by way of specific example, it would have required undue experimentation to make and/or use the invention within the full scope of the invention, as claimed by Applicant.

The Existence of Working Examples

Example 1 describes the general materials and methods used, and it is noted that only a single adenoviral vector is used in the examples: AdCMVp53 (Applicant's elected species of promoter and transgene). Example 2 demonstrates the effect of perfusion rate on virus production and purification, using Applicant's Cellcube^{TM} system. Example 3 demonstrates

methods of harvesting and lysis of vectors. Example 4 demonstrates the effect of concentration/diafiltration on virus recovery. Example 5 demonstrates the effect of salt addition on Benzonase treatment. Example 6 demonstrates ion exchange chromatographic purification of adenoviral vectors. Example 7 demonstrates other purification methods. Example 8 demonstrates AdCMVp53 purification from crude virus generated in Applicant's Cellcube™ system. Example 9 demonstrates improved AD-p53 production in serum-free suspension culture.

However, none of these examples demonstrate a single therapeutic treatment. They also do not overcome any single unpredictability in the art. Hence, even after reviewing Applicant's specification, the Artisan would not be able to reasonably predict, for any particular embodiment, whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment, whether any particular form of p53 except wild-type would be efficacious, and whether immune responses would kill the patient before therapy could be effected.

It is emphasized that the specification only describes a method of purifying adenovirus but does not teach treatment, particularly whether various limitations, such as A260/A280 ratios, level of nucleic acid contamination, etc., would have any effect on the treatment of a disease.

The Quantity of Experimentation Needed to Make and/or Use the Invention

Because of the lack of pertinent working examples, insufficient guidance and direction provided by Applicant, the inherent unpredictability in the art, the state of the art, and the nature

of the invention, even in the face of an advanced level of skill in the art, the Artisan would have been required to perform a large amount of experimentation to make and/or use the invention within its fully-claimed scope.

Such experimentation would be required to reasonably predict whether enough nucleic acid reaches the target cells (*in vivo*) or enough transformed cells reach the target sites and survive (*ex vivo*), the nucleic acid is incorporated into the cells, the nucleic acid transcribes enough stable and functional mRNA, and protein therefrom, to effect treatment, and that such expression occurs for a long enough period of time to effect treatment, whether any particular form of p53 except wild-type would be efficacious, and whether immune responses would kill the patient before therapy could be effected.

Conclusion

Because of the large amount of experimentation required to make and/or use the invention within the full scope of each claim, as claimed by Applicant, such experimentation is considered undue, and therefore, the claims are not enabled for any treatment, any adenovirus, any transgene, or any promoter, except the treatment of cancer by direct administration of an adenoviral vector, comprising a sequence encoding wild-type p53 driven by a promoter, to the tumor.

Art Rejections

With regard to the art rejections, the method of obtaining the adenovirus is not given weight, because the specification provides no reason to believe that the adenoviruses produced by Applicant's methods are materially-different from an adenovirus produced by any other

method. Applicant is directed to *In re Best*, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977), where it is stated:

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product ... Wether the rejection is based on 'inherency' under 35 U.S.C. § 102, on 'prima facie obviousness' under 35 U.S.C. § 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or obtain and compare prior art products [footnote omitted].

Hence, absent evidence to the contrary, Applicant's methods of producing adenoviruses provide for a substantially-identical adenovirus as that manufactured by other processes, and the method of obtaining such adenoviruses is irrelevant for purposes of prior art rejections.

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 70-226 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002.

With regard to Claims 70-72, 80-97, 100-103, 110-128, 131-134, 141-159, 162-165, 172-190, 193-196, 203-221, 224-226, Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Moreover, such adenoviral vectors may lack E1A and/or E1B genes, and be grown in 293 cells (e.g., col. 4, lines 15-32). Furthermore it is desirable that such compositions are substantially pure (e.g., col. 5, lines 1-14). Lastly, such compositions are administered in a pharmaceutically-acceptable buffers (Id.).

With regard to Claims 75-76, 106-107, 137-138, 168-169, 199-200, Applicant states that A260/A280 ratios using Applicant's methods are 1.27+/-0.03, and this is similar to the methods that employ cesium chloride gradients (p. 91, lines 8-11). Moreover, Zhang teaches the use of cesium chloride gradients (col. 5, lines 11-14). Therefore, Zhang inherently teaches the same ratio.

With regard to Claims 78, 109, 140, 171, 202, Applicant teaches that the absence of BSA is an effect of using serum-free media in growing such adenoviruses, and not that it alters the treatment characteristics of the adenoviral vectors, so Applicant's claimed BSA content is not given patentable weight.

With regard to Claims 98-99, 129-130, 160-161, 191-192, 222-223, Zhang teaches that 10-50 PFU per cell will yield growth inhibition due to viral infection and expression of p53 (cols. 13-14, paragraph bridging). Moreover, Zhang teaches using $5x10^7$PFU/mouse (EXAMPLE 6), and changing the PFU administered based on the result desired (EXAMPLE 7).

Therefore, Zhang inherently teaches Applicant's claimed amounts, as those amounts may be desired, for instance, to infect $50x10^{10}$ cells at 50 PFU/cell, one would use 10^{10} PFU.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 73-74, 77, 104-105, 108, 135-136, 139, 166-167, 170, 197-198, and 201 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 6,410,010 to Zhang, et al., filed 29 October 1993, patented 25 June 2002 and U.S. Patent No. 5,837,520 to Shabram, et al, filed 7 March 1995, Patented 17 November 1998.

Zhang teaches the direct administration (e.g., col. 23, lines 8-10) of adenoviral vectors (Id.) comprising the CMV-MIE promoter operably linked to a p53 transgene (EXAMPLE 4) for treating cancer in a mouse (EXAMPLE 6). Applicant also states that A260/A280 ratios using Applicant's methods are 1.27+/-0.03, and this is similar to the methods that employ cesium chloride gradients (p. 91, lines 8-11). Moreover, Zhang teaches the use of cesium chloride gradients (col. 5, lines 11-14). Therefore, Zhang inherently teaches the same ratio.

However, while Zhang teaches that it is preferable to remove all contaminants, including contaminating nucleic acids from unencapsulated adenoviruses (e.g., col. 5, lines 6-14), Zhang does not teach that such purification can yield less 0.8 or 0.2 nanograms/mL.

On the other hand, Shabram teaches that such unencapsulated adenovirus may be removed by Benzonase™ treatment after lysing the cells (EXAMPLE 1).

Therefore, at the time of invention by Applicant, it would have been obvious to the Artisan to modify the methods of preparation of Zhang with the Benzonase™ treatment of Shabram. The Artisan would have been motivated to do so in order to remove the contaminating nucleic acid. Moreover, the Artisan would have had a reasonable expectation of success, as Benzonase™ treatment of Shabram was known to be efficacious in the removal of contaminating nucleic acids, and Zhang had already shown the method of treatment efficacious.

Therefore, in the process of modifying Zhang with the Benzonase™ treatment of Shabram, the Artisan would inherently achieve the contaminating concentrations of nucleic acid that Applicant is claiming.

It is noted that while the cites arts do not teach the precise concentrations claimed by Applicant, there is no evidence of record that such limitation would have altered the steps of treating a cancer and the specification as filed does not teach any more than what is taught in the cited art with respect to the treatment method.

CONCLUSION

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RAM R. SHUKLA, PH.D.
PRIMARY EXAMINER